

High-Sensitivity Cardiac Troponin T Concentrations below the Limit of Detection to Exclude Acute Myocardial Infarction: A Prospective Evaluation

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BACKGROUND: Initial reports suggest that concentrations of high-sensitivity cardiac troponin T (hs-cTnT) (Roche Diagnostics Elecsys[®]) below the limit of blank (LoB) (3 ng/L) or limit of detection (LoD) (5 ng/L) of the assay have almost 100% negative predictive value (NPV) for acute myocardial infarction (AMI), particularly among patients without electrocardiograph (ECG) evidence of ischemia. We aimed to prospectively validate those findings.

METHODS: We included adults presenting to the emergency department with suspected cardiac chest pain. Standard troponin T (cTnT) and hs-cTnT (both Roche Elecsys) were tested in samples drawn on arrival. The primary outcome was AMI, adjudicated by 2 investigators on the basis of clinical data and ≥ 12 -h cTnT testing. We also evaluated diagnostic performance when AMI was readjudicated on the basis of hs-cTnT (≥ 12 -h) concentrations.

RESULTS: Of 463 patients included, 79 (17.1%) had AMI. Twenty-four patients (5.2%) had hs-cTnT concentrations below the LoB, although none had AMI. Ninety-six patients (20.7%) had hs-cTnT concentrations below the LoD, 1 of whom had AMI. Thus, diagnostic sensitivity was 98.7% (95% CI 87.5%–98.6%) and NPV was 99.0% (95% CI 94.3%–100.0%). Of the 17.3% (n = 80) patients with hs-cTnT below the LoD and no ECG ischemia, none had AMI. Thus, diagnostic sensitivity was 100.0% (95% CI 95.4%–100.0%) and NPV was 100.0% (95% CI 95.5%–100.0%). Sensitivity and NPV were maintained when AMI was readjudicated on the basis of hs-cTnT.

CONCLUSIONS: Our findings confirm that patients with nonischemic ECG and undetectable hs-cTnT at presentation have a very low probability of AMI, although the proportion of patients affected was smaller than in previous research.

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High-sensitivity cardiac troponin assays enable troponin concentrations to be quantified in many healthy individuals (1). In the emergency department (ED),⁸ high-sensitivity cardiac troponin has been shown to have greater diagnostic sensitivity at the time of presentation than standard assays (2). However, even with high-sensitivity assays, use of the traditional diagnostic cutoff set at the 99th percentile yields a diagnostic sensitivity of only approximately 90% at the time of presentation, and many studies used less-sensitive gold standards as a comparator, possibly leading to inflated estimates of diagnostic sensitivity by this approach (3). Serial sampling therefore remains necessary for all patients with acute myocardial infarction (AMI) to be identified (4).

It is known that patients with troponin concentrations that are detectable but below the 99th percentile have a worse cardiovascular prognosis than those with undetectable troponin, suggesting that cardiac comorbidities lead to minor increases in high-sensitivity cardiac troponin values even within the reference range (5). We have previously demonstrated that patients with suspected AMI who have undetectable concentrations [below the limit of blank (LoB)] of high-sensitivity cardiac troponin T (hs-cTnT) (Elecsys[®], Roche Diagnostics) at

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⁸ Nonstandard abbreviations: ED, emergency department; AMI, acute myocardial infarction; LoB, limit of blank; hs-cTnT, high-sensitivity cardiac troponin T; LoD, limit of detection; ECG, electrocardiograph; MACE, major adverse cardiac events; PPV, positive predictive value; NPV, negative predictive value; AUC, area under the ROC curve; MACS, Manchester Acute Coronary Syndromes.

the time of presentation to the ED are highly unlikely to have AMI (6). Indeed, the diagnostic sensitivity of this strategy was shown to be 100% (95% CI 95.1%–100.0%) in an initial cohort study of 703 patients and 99.7% (99.1%–100.0%) on subsequent retrospective evaluation of the strategy in a further 915 patients. Among these 1618 patients, only 1 AMI was missed, in a patient who presented within 1 h of symptom onset. This strategy would have enabled AMI to be immediately ruled out in approximately 20% of all patients, obviating the need for serial testing, avoiding the risks of empirical antiplatelet and antithrombotic treatment, and reducing unnecessary hospital admissions. Others have provided similarly positive information, but these types of retrospective studies often have lacked late samples on large numbers of patients (7).

Recognizing the significant potential medical and medicolegal implications of implementing a strategy of a single blood test for early rule-out in clinical practice, we sought for the first time to prospectively evaluate the diagnostic sensitivity and negative predictive value of the use of an hs-cTnT cutoff set at the LoB (3 ng/L) and limit of detection (LoD) (5 ng/L), alone and in combination with electrocardiograph (ECG) findings.

Materials and Methods

We undertook a prospective diagnostic cohort study in the ED at Stepping Hill Hospital, Stockport, UK. The primary objective of the study was to validate a clinical decision rule, which has been reported separately (8). Stepping Hill Hospital is a District General Hospital in northwest England, with approximately 87 000 ED visits per annum. We included consecutive adult patients presenting to the ED with chest pain suspected to be of cardiac origin. Patients requiring hospital admission for a concomitant medical condition were excluded, as well as those with renal failure needing dialysis, significant chest trauma with suspected myocardial contusion, or pregnancy; non-English speakers; prisoners (for ethical reasons); and those in whom all means of follow-up would be impossible. Ethics approval was obtained from the local research ethics committee (09/H1014/74), and all participants provided written informed consent.

All participants underwent testing for both hs-cTnT (fifth-generation Elecsys, Roche Diagnostics; 99th percentile 14 ng/L, CV <10% at 12 ng/L, LoB 3 ng/L, LoD 5 ng/L) and standard troponin T (cTnT, fourth-generation Elecsys, Roche Diagnostics; 99th percentile 0.01 µg/L, CV <10% at 0.035 µg/L, LoD 0.01 µg/L) at the time of arrival in the ED and 12 h after symptom onset. For hs-cTnT and the initial cTnT, serum samples were frozen at –70 °C pending subsequent testing. Aliquots were initially tested after a single freeze–thaw cycle and immediately refrozen at –70 °C. To address the cal-

ibration shift that subsequently became apparent, the same aliquots were retested after a second freeze–thaw cycle. hs-cTnT has been shown to be stable under these conditions (9). Before reporting our initial findings from this work, we became aware that the batch of hs-cTnT reagents used in this study had been affected by a calibration shift (10). We therefore retested aliquots of frozen serum using an unaffected batch. The retested data are reported in this article.

Clinical data were recorded by the treating physician with a custom-designed case report form. ECGs were reported at the time of presentation by the treating physician, who documented the presence or absence of findings consistent with acute myocardial ischemia or infarction. All patients were subsequently followed up by telephone, e-mail, or home visit and by chart review after 30 days.

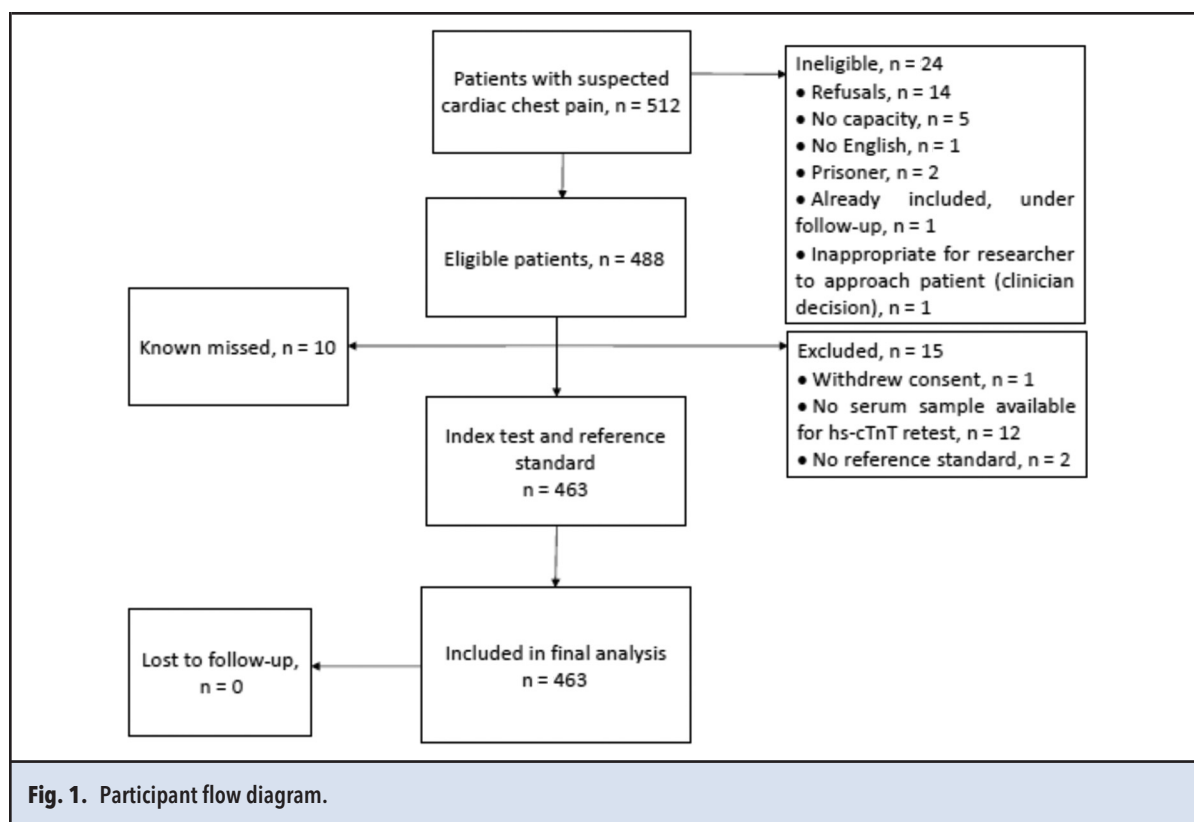
OUTCOMES

Primary outcome. The primary outcome of AMI was adjudicated by 2 independent investigators with all clinical, laboratory, and imaging data (including reference standard 12-h cTnT concentrations) available for review but blinded to investigational assay (hs-cTnT) results. AMI was diagnosed on the basis of a rise and/or fall of cTnT above the 99th percentile, with a minimum change between samples of 0.02 µg/L (on the basis of the analytical characteristics of the assay), in conjunction with the appropriate clinical context, imaging evidence of myocardial infarction, or ischemic ECG changes (11). Disagreements were resolved by discussion.

Secondary outcomes. The secondary outcome of major adverse cardiac events (MACE) within 30 days was defined as death, incident AMI, or the need for coronary revascularization or if the treating cardiologist reported the presence of a coronary stenosis of >50%. Finally, we examined the proportion of patients with hs-cTnT concentrations below each threshold that were given empirical treatment for a presumed acute coronary syndrome in the ED.

STATISTICAL ANALYSIS

We assessed overall diagnostic accuracy of hs-cTnT and cTnT by ROC curve analysis with SPSS version 20.0. Diagnostic sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and likelihood ratios were calculated at the standard 99th percentile cutoffs (hs-cTnT and cTnT), at the LoB of the assay (<3 ng/L, hs-cTnT only), and at the LoD of the assay (5 ng/L, hs-cTnT only) with MedCalc version 13.0.4.0 (MedCalc Software). We compared diagnostic sensitivities, specificities, and paired proportions by McNemar test and calculated confidence intervals for proportions by the modified Wald method (12).



SENSITIVITY ANALYSES

To explore the potential impact on diagnostic accuracy when hs-cTnT is used as the reference standard for AMI, we subsequently readjudicated the diagnosis of AMI on the basis of hs-cTnT concentrations (at presentation and after 12 h). A change of >9.2 ng/L was taken to represent a significant rise and/or fall on serial sampling for these purposes (13). We then evaluated the performance of the initial hs-cTnT concentration for diagnosing AMI on the basis of hs-cTnT concentrations.

In addition, we explored the impact of the calibration shift, which affected the initial batch of reagents we used to test for hs-cTnT, on our findings. To compare the results of the affected and unaffected lots, we created a Bland–Altman plot and ran a Deming regression (MedCalc). We also evaluated diagnostic performance using results from the affected lot.

Results

DIAGNOSING AMI

We included 463 patients, admitted between April and July 2010, in the study (Fig. 1). In total, 17.1% ($n = 79$) patients had AMI on the basis of the cTnT results, of whom 15 had ECG changes compatible with ST-elevation MI (STEMI). Baseline characteristics are

shown in Table 1. The area under the ROC curve (AUC) was 0.95 (95% CI 0.92–0.98) for the admission hs-cTnT concentration to detect these AMIs compared with 0.84 (95% CI 0.78–0.90) for cTnT. The diagnostic sensitivity, specificity, PPV, and NPV of cTnT and hs-cTnT (measured at presentation) for AMI at each diagnostic cutoff are shown in Table 2. At the standard 99th percentile cutoff, hs-cTnT had significantly higher diagnostic sensitivity than cTnT ($P < 0.0001$).

In this study, only 24 (5.2%) patients had hs-cTnT concentrations below the LoB (<3 ng/L). None of those patients were subsequently diagnosed with AMI. Ninety-six (20.7%) patients had a hs-cTnT concentration below the LoD for the assay (5 ng/L). Of those patients, only 1 (1.0%) had AMI. That patient presented within 30 min of symptom onset with ECG evidence of a posterior STEMI and was immediately sent to the catheter laboratory for primary percutaneous coronary intervention.

Combining presentation hs-cTnT concentrations with ECG findings, 4.8% ($n = 22$) patients had a hs-cTnT concentration <3 ng/L and no ECG evidence of acute ischemia (none had AMI); 17.3% ($n = 80$) patients had both a hs-cTnT concentration <5 ng/L and no ECG evidence of acute ischemia (none had AMI); and 51.0% ($n = 236$) patients had a hs-cTnT concentration <14

Variable	Total	AMI	No AMI
n	463	79	384
Age, years	64 (16)	72 (14)	62 (15)
Men	270 (58.3)	50 (63.3)	220 (57.3)
Previous angina	186 (40.2)	24 (30.4)	162 (42.2)
Previous MI ^b	139 (30.0)	28 (35.4)	111 (28.9)
Hypertension	197 (42.5)	42 (53.2)	155 (40.4)
Hyperlipidaemia	186 (40.2)	35 (44.3)	151 (39.3)
Diabetes mellitus	80 (17.3)	20 (25.3)	60 (15.6)
Smoking	96 (20.7)	18 (22.8)	78 (20.3)
Family history of coronary heart disease ^c	171 (36.9)	22 (27.8)	149 (38.8)
Previous coronary intervention	102 (22.0)	15 (19.0)	87 (22.7)
Peripheral vascular disease	15 (3.2)	2 (2.5)	13 (3.4)
Cerebrovascular disease	30 (6.5)	4 (5.1)	26 (6.8)
Chronic renal impairment	17 (3.7)	3 (3.8)	14 (3.6)
Time from symptom onset			
≤3 h	212 (45.8)	33 (41.8)	179 (46.6)
3.01–6 h	94 (20.3)	19 (24.1)	75 (19.5)
6.01–12 h	64 (13.8)	11 (13.9)	53 (13.8)
>12 h	93 (20.1)	16 (20.3)	77 (20.1)

^a Data are mean (SD) or n (%).
^b Data missing in 1 patient.
^c Data missing in 12 patients.

ng/L and no ECG evidence of ischemia, of whom 1 (0.4%) had AMI. The diagnostic sensitivity, specificity, PPV, and NPV of the combination of hs-cTnT and admission ECG are shown in Table 2.

SENSITIVITY ANALYSES

On readjudication on the basis of 12-h hs-cTnT concentrations, 16.6% of patients (n = 77) were assigned a diagnosis of AMI. The diagnostic characteristics of the

Assay and cutoff	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
cTnT				
0.01 µg/L ^a	70.9 (59.6–80.6)	92.7 (89.6–95.1)	66.7 (55.5–76.6)	93.9 (91.0–96.1)
hs-cTnT				
14 ng/L ^a	94.9 (87.5–98.6)	72.4 (67.6–76.8)	41.4 (34.2–49.0)	98.6 (96.4–99.6)
5 ng/L ^b	98.7 (93.2–100.0)	24.7 (20.5–29.4)	21.3 (17.2–25.8)	99.0 (94.3–100.0)
3 ng/L ^c	100.0 (95.4–100.0)	6.3 (4.1–9.2)	18.0 (14.5–21.9)	100.0 (85.8–100.0)
14 ng/L and no ECG ischemia ^d	98.7 (93.2–100.0)	61.2 (56.1–66.1)	34.4 (28.2–40.9)	99.6 (97.7–100.0)
<5 ng/L and no ECG ischemia ^d	100.0 (95.4–100.0)	20.8 (16.9–25.2)	20.6 (16.7–25.0)	100.0 (95.5–100.0)
<3 ng/L and no ECG ischemia ^d	100.0 (95.4–100.0)	5.7 (3.6–8.6)	17.9 (14.5–21.8)	100.0 (83.9–100.0)

^a Cutoff set at the 99th percentile of a reference population.
^b Cutoff set at the limit of detection of the assay.
^c Cutoff set at the limit of blank of the assay.
^d AMI ruled out only if both conditions met.

Table 3. Diagnostic sensitivity and specificity of presentation hs-cTnT and cTnT for MACE within 30 days at the different cutoffs studied, with and without incorporation of initial ECG findings.

Assay and cutoff	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
cTnT				
0.01 µg/L ^a	62.2 (51.9–71.8)	93.7 (90.7–96.0)	72.6 (61.8–81.8)	90.2 (86.8–93.0)
hs-cTnT				
14 ng/L ^a	89.8 (82.0–95.0)	74.5 (69.7–78.9)	48.6 (41.1–56.2)	96.5 (93.6–98.3)
5 ng/L ^b	99.0 (94.5–100.0)	26.0 (21.6–30.9)	26.4 (22.0–31.3)	99.0 (94.3–100.0)
3 ng/L ^c	100.0 (96.3–100.0)	3.6 (2.3–5.3)	13.3 (10.9–15.9)	100.0 (85.8–100.0)
14 ng/L and no ECG ischemia ^d	94.9 (88.5–98.3)	63.3 (58.1–68.2)	41.0 (34.5–47.7)	97.9 (95.1–99.3)
<5 ng/L and no ECG ischemia ^d	100.0 (96.3–100.0)	21.9 (17.8–26.5)	25.6 (21.3–30.3)	100.0 (95.5–100.0)
<3 ng/L and no ECG ischemia ^d	100.0 (96.3–100.0)	6.0 (3.8–9.0)	22.2 (18.4–26.4)	100.0 (84.6–100.0)

^a Cutoff set at the 99th percentile of a reference population.
^b Cutoff set at the limit of detection of the assay.
^c Cutoff set at the limit of blank of the assay.
^d AMI ruled out only if both conditions met.

admission hs-cTnT concentrations with cutoffs at the LoB and LoD were unchanged. Of 24 patients with an initial hs-cTnT <3 ng/L and 96 patients with hs-cTnT <5 ng/L, 0 and 1, respectively, had an adjudicated diagnosis of AMI. Again, of the 17.3% (n = 80) patients who had both an hs-cTnT concentration <5 ng/L and no ECG evidence of acute ischemia, none had AMI, giving a diagnostic sensitivity of 100.0% (95% CI 95.3%–100.0%) and NPV 100.0% (95% CI 95.5%–100.0%).

A comparison of the results obtained when using the affected and unaffected lots of hs-cTnT reagent is presented in Supplemental Figs. 1 and 2, which accompany the online version of this article at <http://www.clinchem.org/content/vol61/issue7>. In total, 853 paired measurements were available from 465 patients (including 2 patients who had an admission sample but were excluded from the primary analysis because reference standard delayed troponin testing did not take place to enable adjudication of AMI).

The prevalence of AMI was identical with the affected and unaffected lots because we did not find any discrepancies at the 99th percentile cutoff. With the affected batch, 119 of 463 patients (25.7%) had hs-cTnT concentrations <3 ng/L compared with 24 (5.2%) with the unaffected batch (absolute difference 20.5%, $P < 0.0001$). In total, 181 (39.1%) patients had hs-cTnT concentrations <5 ng/L with the affected batch compared with 96 (20.7%; absolute difference 18.4%, $P < 0.0001$).

The diagnostic accuracy of the affected lot is presented in online Supplemental Table 1. Overall, diagnostic accuracy was similar with each lot. For diagnosing AMI, the area under the ROC curve of the admission sample was 0.95 for both the affected and unaffected lots.

At the LoB, the affected lot would have missed 1 AMI, and at the LoD, 2 AMIs would have been missed. However, both patients had ECG evidence of ischemia, meaning that diagnostic sensitivity remained 100% for the combined approach.

PREDICTION OF OUTCOMES

After 30 days, a total of 21.2% (n = 98) patients had developed 1 or more MACE (including the 79 patients with an initial adjudicated diagnosis of AMI). At 30-day follow up, an additional 1.3% (n = 6) patients had died (all cardiac or presumed cardiac); 2.6% (n = 12) had incident AMI, and 11.9% (n = 55) underwent coronary revascularization or had a new angiographic stenosis identified by 30 days. The diagnostic performance of the presentation hs-cTnT for detection of MACE at 30 days for each cutoff studied is shown in Table 3.

The sensitivity and specificity of the diagnostic strategies evaluated for predicting MACE within 30 days is shown in Table 3. None of the 24 patients (95% CI 0.0%–16.3%) with hs-cTnT <3 ng/L developed MACE within 30 days, and 1 patient (1.4%, 95% CI 0.0%–6.2%) with hs-cTnT <5 ng/L (the patient with posterior STEMI as described above) developed MACE within 30 days. In all, 3.6% (95% CI 1.9%–6.5%, n = 10) of patients with an admission hs-cTnT concentration <14 ng/L developed MACE within 30 days. For patients with an initial hs-cTnT concentration <3 ng/L, the median length of stay was 2 days (interquartile range 1.25–2.0 days), which represents an average of 1 night in the hospital, and 2 days (interquartile range 1.0–2.0) for patients with an initial hs-cTnT <5 ng/L (Table 4).

Table 4. Length of stay according to initial hs-cTnT.^a

Initial hs-cTnT value	Length of stay, days
All	2 (2-7)
<5 ng/L	2 (1-2)
5-13.99 ng/L	2 (2-3)
≥14 ng/L	6 (3-12)

^a Data are median (interquartile range).

Discussion

For the first time in a prospective study, we have validated that an AMI can be ruled out by a single blood test at the time of initial presentation with extremely high negative predictive value in patients with very low hs-cTnT concentrations. These data fill an important void, since none of the prior studies had complete ascertainment of late samples, and thus late concentration increases were possible. However, only 5.2% of patients had values below the LoB (3 ng/L) of the assay. Use of the LoD (5 ng/L) as a cutoff also had high negative predictive value (99.0%) but would have missed 1 AMI in a very early presenter in whom the AMI was diagnosed on ECG.

If this strategy were applied to patients without ECG evidence of ischemia/infarction, use of the LoD cutoff could have enabled the immediate discharge of 17.3% patients with 100% negative predictive value. Taken in conjunction with the similar findings previously reported (although late values were rarely available in that study) (7), this work confirms the potential value of using low hs-cTnT concentrations to facilitate safe early discharge in practice.

Our data also provide information concerning the mechanisms of this effect. It may be true that this strategy takes advantage of the high sensitivity of the assay being used to detect cardiac injury at an early point in time. However, those individuals without cardiac comorbidities are known to have lower values of hs-cTnT, even below the 99th percentile upper reference limit. Thus, this approach may work in part by identifying a population that is at low risk for the development of cardiovascular events at baseline as well as the early detection of acute cardiac injury. Hospitals in which larger numbers of young and other low-risk individuals are evaluated may find this approach even more attractive. These differences may be the reason for the much lower frequency of low values in our study compared with the Bandstein et al. study (7).

The proportion of patients eligible for early discharge may be greater when troponin concentrations are combined with other clinical information as part of a clinical decision rule such as the Manchester Acute Coronary Syndromes (MACS) decision rule, which has been validated prospectively in this cohort (14), or as part of a

multimarker strategy. For example, use of the LoD of a high-sensitivity cardiac troponin I assay and plasma glucose has been reported to have a 100% diagnostic sensitivity to rule out AMI (15).

The implications of this strategy would be that patients with a hs-cTnT concentration >5 ng/L and no ECG ischemia would not necessarily have AMI ruled in but would undergo serial troponin testing, at which point further patients could have the diagnosis ruled out. Although there may be some patients who rule in late after symptom onset, very low, unchanging hs-cTnT values over just a few hours may rule out much of the remainder of this population.

We have also presented data regarding the impact of a calibration shift in hs-cTnT reagents on the results at low troponin concentrations. Our findings suggest that the calibration shift is likely to have had little impact when results were dichotomized at the 99th percentile. However, we did note an impact at low troponin concentrations. In particular, the proportion of patients with concentrations below the LoD fell significantly when an unaffected batch was used. This highlights the importance of noting whether affected lots were used when interpreting the findings of previous research evaluating cutoffs below the 99th percentile. The results of investigations using affected reagents should be interpreted with caution, as external validity may be limited. Notably, these findings agree with those reported by Kavsak et al. in a retrospective review of hs-cTnT concentrations measured with unaffected and affected lots over time (16). In that study, the proportion of patients with detectable troponin concentrations fell with the affected lots, suggesting a downward shift at low concentrations. However, there was no significant change in the proportion of patients who had hs-cTnT concentrations above the 99th percentile, again suggesting that the clinical impact of the calibration shift at that cutoff is minimal (16).

Several limitations are noted. Although these data are the first prospective data with this assay, they are observational and as such demonstrate the efficacy rather than the effectiveness of the rule-out strategies evaluated. To determine the true effects of the rule-out strategy when used in practice, interventional trials will be necessary. Second, the data presented here are from a single center. It remains necessary to consider the findings at other centers with different populations to ensure external validity. Third, in this study a lower proportion of patients had an undetectable troponin than in previous work. This may be due to differences in patient cohorts or between-batch variation in hs-cTnT reagents. The latter warrants further investigation.

There have also been concerns about the precision of troponin assays at low concentrations below the 99th percentile as well as other interferences such as hemolysis (17). Although the findings from cohort studies such as

this provide reassurance that this analytical imprecision has little impact on diagnostic sensitivity and NPV, a solution must be found to the challenges this poses to laboratory quality control. As assays with greater analytical sensitivity and precision are developed, it will also be important to determine whether cutoffs above the LoD of such assays can be used to safely rule out AMI.

Finally, although our primary outcome was a diagnosis of AMI adjudicated on the basis of the results of a standard-generation troponin assay, we have overcome this limitation with hs-cTnT values from 12 h, which still demonstrated that diagnostic sensitivity and NPV are maintained.

In conclusion, our findings confirm that patients who have no ECG evidence of ischemia and an hs-cTnT concentration below the LoD at the time of presentation to the ED have a very low probability of AMI, which may be considered to rule out that diagnosis. This strategy could have enabled exclusion of AMI in 17.3% of all patients, although, were other clinical information taken into account, the actual proportion discharged might be lower. Admission hs-cTnT combined with other clinical information as part of a clinical decision rule or serial hs-cTnT sampling over 1–3 h may facilitate safe early discharge of an even greater proportion of patients from ED.

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